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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,327	06/21/2006	Michel Schneider	BR-035 PUS 01	4727

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,327	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *16,17,25,26,31-40,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18-24,27-30,41,42 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/06, 9/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 5/18/2010 is acknowledged. The traversal is on the ground(s) that contrary to the Examiner's assertion, all of the pending claims do share a special technical feature: all require an assembly comprising a gas-filled microvesicle bearing a first overall net charge and a component associated with said microvesicle wherein said component is a supermolecular structure formed by the association of a plurality of molecules, which bears a second overall net charge opposite in sign to said first net charge, comprises a biocompatible surface active agent and has a diameter of 100 nm or lower. Applicant asserts that Unger (US 7,083,572) does not teach a component to be associated with a microvesicle comprising a biocompatible surface agent, only teaching DNA or drug molecules, and that the instant claims require that the component is a supermolecular structure formed by association of a plurality of molecules (comprising surface active agent molecules).

This is not found persuasive because lack of unity can still be shown with regard to the amended claims by US 2004/0146462.

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an

international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature", should be considered with respect to novelty and inventive step.

The common technical feature in all the groups is “an assembly comprising a gas-filled microvesicle bearing a first overall net charge and a component associated with said microvesicle wherein said component is a supermolecular structure formed by the association of a plurality of molecules, which bears a second overall net charge opposite in sign to said first net charge, comprises a biocompatible surface active agent, and has a diameter of 100 nm or lower.” This element cannot be a special technical feature under PCT Rule 13.2 because the element is shown in the prior art.

Eriksen (US 2004/0146462) teaches a combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible

component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). The emulsion component is considered to be within the scope of the instantly claimed "supermolecular structure formed by the association of a plurality of molecules," and Erikson teaches that emulsion particle size can be as small as 0.1 micron (paragraph 0046).

As a result, no special technical features exist among the different groups because the invention in Group 1 fails to make a contribution over the prior art with respect to novelty or inventive step. In conclusion, there is lack of unity of inventions, and therefore restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

The election of the following species is also acknowledged: i) lipid bearing positive charge, in particular DSTAP; ii) and iii) propylene glycol modified phospholipid.

Status of Claims

Claims 1-45 are pending, of which claims 31-40, 43 and 44 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 16, 17, 25 and 26 are withdrawn from consideration as being drawn to non-elected species. Claims 1-15, 18-24, 27-30, 41, 42 and 45 are readable upon the elected invention and species and are examined herein on the merits for patentability.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15, 18-24, 27-30, 41, 42 and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/584,382. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an assembly comprising a gas-filled microvesicle bearing a first overall net charge and a component associated with said microvesicle wherein said component is a supermolecular structure formed by association of a plurality of molecules, which bears a second overall net charge opposite in sign to said first net charge and comprises a biocompatible surface active agent. In the instant claims, the component has a diameter of 100 nm or lower, and in the '382 application, the component has a diameter of 300 nm or lower (claim 8). Both sets of claims include limitations that the component includes a targeting ligand or diagnostic, such as in claim 1 of the '382 application and claim 4 of the instant application. Accordingly, the claims are overlapping in scope and are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4-15, 18, 19, 27-30 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen *et al.* (US 2004/0146462).

Eriksen teaches a combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). The emulsion component is considered to be within the scope of the instantly claimed "supermolecular structure formed by the association of a plurality of molecules." Peptide containing emulsions including surfactants are disclosed in the examples (Table 1, e.g. preparation 24). See

also Examples 10-27 including negatively charged perfluorobutane gas microbubbles (stabilized by hydrogenated phosphatidylserine) and positively charged emulsions; especially Ex. No 15. Therapeutic agents are disclosed as part of the preparation (claim 20). Emulsion particles as small as 0.1 micron are disclosed (paragraph 0046).

With regard to claim 5, distearoylphosphatidylcholine is also included emulsions comprising positively charged surface material and are considered to be "bioactive" in that the component functions as a surfactant in a biological system (paragraph 0154).

With regard to claim 6, preparation 2 is disclosed, including microbubbles comprising 1,2-distearoyl-3-trimethyl-ammoniumpropane and distearoylphosphatidylcholine, which are considered to be "bioactive" in that the component functions as a surfactant in a biological system.

With regard to claims 9-11, 0.2 μl gas/kg body weight negatively charged perflurobutane gas dispersion was combined with 0.1 μl gas/kg body weight positively charged perfluorodimethylcyclobutane emulsion.

Eriksen does not exemplify a supermolecular structure having a particle size of 100 nm.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide preparations as disclosed by Eriksen in which the emulsion component has a particle size around 100 nm. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Eriksen teaches that emulsion particles may be as small as 0.1 micron in order to facilitate unimpeded passage through the pulmonary system. With regard to claims 28-

30, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive of the zeta potential of the assembly, and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Eriksen teaches compositions meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that such formulations would be capable of achieving claimed functional property (zeta potential).

Claims 1-15, 18-24, 27-30, 41, 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider *et al.* (US 6, 258,378) in view of Eriksen *et al.* (US 2004/0146462), in further view of Unger (US 2002/0159952).

Schneider teaches drug containing liposomes to selected areas in the organism and subsequently breaking or opening the liposomes to release the encapsulated content at a given site. In this method, the potential energy-containing agent to be used in association with the liposome vesicles and whose energy can be liberated at will to assist releasing the liposome encapsulated content consists of microparticles

(microbodies) with confined air or gas. The microparticles are preferably air-or gas-filled microspheres, micro-vesicles, or microcapsules, more preferably air- or gas-filled microbubbles or microballoons. When air or gas-filled microspheres in close vicinity to liposome vesicles are caused to break or explode, the liberated cavitation energy will spread around and assist in opening the liposome membrane to free the encapsulated content or by changing the membrane permeability to enhance the drug diffusion. The triggering pulses of, for instance, radio or sound energy to burst the microspheres or microcapsules filled with the confined gas need not be as energetic as those required for directly acting on the liposomes membrane, hence the impact on nearby tissues is reduced. Liposomes optionally comprise targeting ligands (column 2, lines 15-45). The internal volume of the microbubbles is limited by the gas/liquid interface, or in other words, the microbubbles are only bounded by an envelope involving the molecules of the liquid and surfactants loosely bound at the gas to liquid interface or boundary. In the present invention, the surfactants preferably comprise one or more phospholipids at least in part in laminar or lamellar form. The term "lamellar form" indicates that the surfactants are in the form of thin films involving one or more molecular layers ("laminate" form). Particularly preferred are the phospholipids selected from neutral phospholipids such as hydrogenated phosphatidyl choline (HSPC), dipalmitoyl-, distearoyl- and diarachidoyl phosphatidylcholine (DPPC, DSPC, DAPC); negatively charged phospholipids such as dipalmitoyl and distearoyl phosphatidic acid (DPPA, DSPA), dipalmitoyl and distearoyl phosphatidylserine (DPPS, DSPS), dipalmitoyl and distearoyl phosphatidylglycerol (DPPG, DSPG); reactive phospholipids such as

phosphatidyl ethanolamine derivatives coupled to a polyethylenglycol, a biotinyl, a glutaryl, a caproyl or a succinyl amine (column 4). The gas-filled microspheres may be more or less closely associated with the liposomes, i.e. they may simply be admixed with the liposome vesicles whereby they will statistically distance from each other. Alternatively, the liposome vesicles and the gas-filled microspheres can be organised to have affinity for each other, for instance they may each be provided with the molecular components of a conjugate pair. As an example, an antigen may be incorporated in the liposome membrane and an antibody in the microspheres, or vice-versa, so that antigen-antibody conjugation will cause the microspheres and the liposome vesicles to couple with each other. Other coupling systems include lipids (column 5-6). Particularly preferred embodiments of the present invention involve liposomes which comprise three components: A. a neutral lipid, for example, a nonionic or zwitterionic lipid or their derivatives; B. a negatively or positively charged lipid, and C. a lipid bearing a functional component, for example N-biotinyl-PE or PEG-PE. Cholesterol or cholesterol derivatives can be used to replace a part of component A, as generally known to the skilled person (column 6, lines 20+).

Schneider does not specifically recite that microbubbles are associated with liposomes by electrostatic interaction between positively or negatively charged microbubbles with liposomes having opposite charge.

Eriksen teaches combined preparation for simultaneous, separate or sequential use as a contrast agent in ultrasound imaging, said preparation comprising: i) a first composition which is an injectable aqueous medium comprising dispersed gas and

material serving to stabilise said gas; and ii) a second composition which is an injectable oil-in-water emulsion wherein the oil phase comprises a diffusible component capable of diffusion in vivo into said dispersed gas so as at least transiently to increase the size thereof, said composition further comprising material serving to stabilise said emulsion, characterised in that material present at the surfaces of the dispersed gas phase and material present at the surfaces of the dispersed oil phase have opposite charges and thereby have affinity for each other (claim 1). The efficacy of contrast agent preparations may be substantially enhanced if the two compositions are formulated in such a way that the dispersed gas component and diffusible component have affinity for each other, for example as a result of attractive electrostatic or other physical forces or of chemical (including biological) binding. This may be achieved by formulating the dispersed gas component as a stabilised gas dispersion and the diffusible component as a stabilised emulsion such that material present at the surfaces of the dispersed gas has affinity for material present at the surfaces of the dispersed diffusible component. The surface materials having affinity for each other may, for example, be materials such as surfactants which serve to stabilise the gas and diffusible component dispersions. Alternatively, surface materials with appropriate mutual affinity may be mixed with, chemically linked to or otherwise associated with non-affinity stabilising materials in the respective dispersions (paragraph 0015).

Unger teaches that vesicles formed from lipids as stabilizing material include micelles, liposomes, etc., which can be used for carrying therapeutic materials (see paragraphs 0041, 0184, 0202).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide microbubbles having predominantly cationic or anionic phospholipids which are associated with liposomes (or micelles) having a phospholipids of the opposite charge when the teachings of Schneider are taken in view of Eriksen and Unger. Schneider teaches that either microbubble and/or liposome can be prepared using predominantly cationic or anionic phospholipids, and teaches that liposome vesicles and the gas-filled microspheres can be organised to have affinity for each other, including via coupling systems such as lipids. While Schneider does not specifically recite that lipids having electrostatic interaction is a method for coupling, one would have been motived to provide electrostatic interaction between the microbubble and liposome charged components since it is known in the art from Eriksen that a dispersed gas component and another phospholipid stabilized vesicle (emulsion) may have affinity for each other as a result of attractive electrostatic or other physical forces or of chemical (including biological) binding, and that inclusion of oppositely charged components may provide increased interaction and stability between the components. With regard to claim 20, it would have been further obvious to employ charged micelles as equivalent to liposomes as taught by Scheider, since Unger teaches that micelles and liposomes are functionally equivalent vesicles for incorporation and delivery of therapeutic agents.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS